CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 50-781

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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NDA:	50-781
Applicant:	OraPharma, Inc.
Name of Drug:	Minocycline PTS, 1mg.
Indication:	Adjunctive therapy to scaling and root planing procedures for the reduction of pocket depth in patients with adult periodontitis
Documents Reviewed:	Volumes 101 – 121, dated 2/29/00, CD containing data and SAS output.
Medical Officer:	Clarence C. Gilkes, D.D.S./John Kelsey, D.D.S., M.B.A. (Team Leader).
Statistical reviewer	M. Atiar Rahman, Ph.D.

1. Introduction

IND # —— for Minocycline was originally filed on ———— , by Lederle Laboratories, a Division of American Cyanamid Company, who conducted the phase 1 and phase 2 studies during 1988-1991. Lederle Laboratories requested inactivation of IND #—— on January 16, 1997. A transfer of this IND to OraPharma Inc. took place on January 17, 1997. OraPharma, Inc. submitted reports of two phase 3 studies 103A, and 103B to support the claim that the use of Minocycline PTS for 9 months is safe and effective in the treatment of adult periodontitis for the reduction of pocket depth. This document contains the statistical review of the sponsor's reports of the phase 3 studies.

2. Descriptions of the phase 3 studies

Both study 103A and study 103B were randomized, multicenter, single blind with three parallel treatment arms. The treatment arms were as follows:

Arm 1: Scaling and root planing (S/RP) plus subgingival application of Minocycline PTS 1 gm (Minocycline PTS)
Arm 2: S/RP plus subgingival application of vehicle (Vehicle) and
Arm 3: S/RP alone (S/RP)

For entry to the study, among other criteria, a patient had to have at least four teeth with periodontal pocket depth (PD) of 6-9 mm, with bleeding upon probing (BOP).

Reviewer's comment: There were three randomized patients, two in study 103A (patient numbers 1010070 and 1090971) and one in study 103B (patient number 2070791) with baseline PD=5 mm. All these 3 patients were randomized to vehicle arm.

Patients were randomized to one of the three treatment arms following a randomization schedule of block size 3, stratified by center and smoking status. Patients were identified by a 7-digit patient identification number.

The primary clinical aim was to show significant superiority (at 0.05 level of significance) of Minocycline PTS over S/RP in each study. The secondary comparison of Minocycline with vehicle was aimed to show a directional trend of superiority (at 0.20 level of significance) favoring the active in each study.

The sponsor's sample size calculation was based on results published by Jeffcoat et al. [Jeffcoat et al. Multicenter evaluation of a biodegradable chorohexidine/gelatin chip for the treatment of adult periodontitis. J. Dent. Res. 76:1110, 1997]. The authors reported a mean 9-month PD reduction of .69 mm and a standard deviation (SD) of 0.748 mm for patients treated with S/RP plus placebo. Using one-half of this SD (0.374) as δ (clinically meaningful difference in efficacy between treated and controlled arms), α=0.05 (two-sided), and β=0.08 (i.e. 92% power) a sample size of 95 patients per arm was estimated. Allowing 15% loss to follow-up, at least 109 patients per arm (total of at least 327) were planned to be recruited.

In study 103A there were 9 centers recruiting a total of 368 patients. In study 103B there were also 9 centers recruiting a total of 380 patients. Sponsor's summary tables describing centers and number of recruited patients are given in Tables 1A and 7A in the appendix for studies 103A and 103B, respectively.

3. Efficacy endpoints

The primary efficacy endpoint was the change from baseline in within subject average pocket depth (PD) at 9 months. A pocket depth is measured from the free gingival margin to the base of the pocket. In measuring a PD any fractional reading was ignored.

Secondary efficacy end points included the following:

1. Clinical response: For each patient clinical response is defined as the percentage of baseline treatment sites with ≥1 mm improvement, ≥2 mm improvement, and ≥3 mm improvement at 9 months.

2. PD Extent scores: For each patient PD extent score is defined as the percentage of baseline treatment sites with average PD≥ 5 mm, average PD≥ 6 mm and average PD≥ 7 mm at each visit.

3. Bleeding on probing: Percentage of baseline treatment sites with bleeding on probing at each visit. The variable had a value equal to 0 if there was no bleeding or 1 if there was bleeding within 10 seconds after probing.

4. Clinical Attachment Level: The clinical attachment level, distance from the cemento-enamel junction to the base of the pocket, was measured as a safety parameter.

5. Need for rescue[1]: Total number of rescued teeth in 9 months in each treatment group.

4. Data analysis plan

The following was the sponsor's data analysis plan for primary and secondary efficacy end points.

For the primary efficacy analysis the patient was the unit of analysis. The patients mean PD changes from baseline at 9 months were analyzed using the method of analysis of covariance (ANCOVA). The ANCOVA model included treatment group, pooled center[2], disease severity, and smoking status as factors, and baseline PD and age as covariates.

A supportive analysis was performed using the covariance adjusted Cochran-Mantel-Haenszel (CMH) test. This was done using a two step procedure. In the first step a multiple regression was run on the site-specific data using baseline PD, disease severity, and age in the model. The site-specific residuals from the multiple regression were used to generate standardized rank scores. The site-specific standardized rank scores were then averaged by patient to create composite standardized rank scores. In the second step, the CMH test was performed on the composite rank scores, stratified by center and smoking status.

The primary efficacy analyses were based on ITT population, defined as all randomized patients with post-treatment PD evaluation on at least one tooth. Additional analysis was performed on evaluable patients, defined as all ITT patients who completed scheduled treatment on all non-rescued treatment teeth at both the 3 and 6-month visits, and had end point assessments within the 9-month visit window on at least one previously non-rescued treatment tooth. Further, patients who became 'complete rescued' (i.e., either whole-patient rescued, or the last non-rescued treatment tooth was rescued) were included in the evaluable sample provided they met the scheduled treatment and assessment conditions up to the time they became complete rescue.

Reviewer's comment: The Division recommends to define the ITT population as patients who were randomized and dispensed the study medication (active or placebo). The reviewer checked the ITT population for both studies (103A and 103B) following the Division's recommended definition. This ITT population coincided with the sponsor's ITT populations. Therefore, the results remain unchanged.

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[1] If a site exhibited a PD increase of 3 mm or more, relative to baseline, during the study (regardless of treatment), the entire tooth was discontinued from the study. The affected tooth was rescued with local treatment consisting of S/RP and was monitored clinically. A patient with a rescued tooth was considered to have completed the study at the time of rescue. For such patient, each treated tooth was evaluated at the time of event on a tooth by tooth basis.

[2] Originally there were 9 centers. Centers with less than one third of the number of patients in the largest center were considered as small centers. Such centers were pooled together (smallest to the next largest) until all centers had at least one third of the number of patients in the largest center. At the end of the process the remaining centers were known as the pooled centers. There were 8 pooled centers in each of the studies.

The analysis plans for the secondary efficacy endpoints were similar to that of the primary efficacy, that is using the ANCOVA method. Additional analyses were performed using the CMH tests.

5. Patient withdrawal and handling missing values

As stated by the sponsor missing values in both study 103A and 103B occurred due to three reasons 1) due to rescue procedure, 2) discontinuation due to lack of efficacy, and 3) discontinuation due to AEs, or loss to follow-up due to unknown causes. A patient with a rescued tooth was considered to have completed the study at the time of rescue. For such patient, each treatment tooth was evaluated at the time of event on a tooth by tooth basis. To impute the missing values the sponsor used the method of last (pre-rescue) observation was carried forward (LOCF) for teeth not needing rescue, and worst observation carried forward (WOCF) for teeth needing rescue. The Method of LOCF was followed for patients who discontinued due to lack of efficacy or AEs. A treated tooth lost between visits, regardless of cause, had the WOCF for each missing post-loss assessment. For patients who discontinued due to unknown reasons, LOCF was done to impute the missing values. A summary table prepared by the sponsor showing number of withdrawal patients by withdrawal categories is given in Tables 2A and 8A in the appendix for studies 103A and 103B, respectively.

Reviewer's comment: Total number of withdrawals and missing values, summarized by the reviewer in different treatment groups, are given in Table 1.

Table 1. Number of withdrawal patients and missing values

	103A			*103B*		
	Minocycline	*Vehicle*	*S/RP*	*Minocycline*	*Vehicle*	*S/RP*
	121	*123*	*124*	*128*	*126*	*126*
Total Patient Withdrawal	*6 (5.0%)*	*11 (8.9%)*	*10 (8.1%)*	*6(4.7%)*	*8(6.35%)*	*11(8.7%)*
Missing values at visit 3	*3*	*3*	*4*	*0*	*2*	*4*
Missing values at visit 4	*4*	*9*	*6*	*2*	*3*	*6*
Missing values at visit 5	*5*	*10*	*8*	*5*	*7*	*8*
Missing values at visit 6	*5*	*9*	*10*	*6*	*8*	*11*
Total missing values	*17*	*31*	*28*	*13*	*20*	*29*

Reviewer's analysis using the Fisher exact test did not show statistically significant difference in the percentage of withdrawal patients among treatment groups.

6. Results of data analysis (Study 103A)

6.1 Demographic parameters

Table 3A in the appendix shows the sponsor's summary of demographic parameters. The sponsor did not perform statistical analysis to compare the demographic parameters.

Reviewer's comment: Table 3A shows that the Minocycline PTS group had a relatively higher percentage of patients with more than 50 years of age compared to vehicle or S/RP (41.3% 35.0%, and 33.1% in Minocycline PTS, vehicle, and S/RP, respectively).

The Fisher Exact tests performed by the reviewer did not show the differences in these percentages to be statistically significant.

6.2 Primary efficacy analysis

6.2.1 Analysis of PD change from baseline in the ITT patients

Table 2 shows the sponsor's results of the analysis of the primary efficacy endpoint, change from baseline in PD, in ITT population.

Table 2: Comparisons of mean change from baseline in PD at 9 months in ITT population using ANCOVA (Study 103A)

PATIENT'S AVERAGE POCKET DEPTH	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 121	VEHICLE 123	S/RP 124	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
BASELINE	n	121	123	124	0.870	0.571
	MEAN (STD DEV)	5.88 (0.45)	5.91 (0.54)	5.88 (0.50)		
	MEDIAN	5.78	5.74	5.73		
	RANGE					
CHANGE FROM BASELINE MONTH 9	n	121	123	124	0.045	<.001
	MEAN (STD DEV)	-1.20 (0.79)	-0.90 (0.70)	-1.04 (0.81)		
	MEDIAN	-1.18	-0.77	-0.99		
	RANGE					

Source: Table 3.2.1, p. 100, vol. 101 of the sponsor's submission

The results show statistically significant mean reduction in PD in the Minocycline PTS group compared to both vehicle and S/RP. The magnitude of mean reduction in PD in Minocycline PTS group is 0.16 mm over that of S/RP and 0.30 mm over that of vehicle.

Additional non-parametric analysis of the primary efficacy endpoint using the CMH test by the sponsor produced a p-value of 0.057 when Minocycline PTS was compared to S/RP and a p-value of 0.001 when Minocycline PTS was compared to vehicle.

Reviewer's comments:

1. ***The reviewer's analysis of the primary efficacy end point confirmed the sponsor's results.***

2. ***As was mentioned in Section 4, for analysis of primary efficacy the sponsor used the method of ANCOVA with treatment group, pooled center, disease severity, and smoking status as factors and baseline PD and age as covariates. However, sponsor's results showed that the effects of disease severity and baseline PD were not statistically significant. Therefore, a reanalysis of the primary efficacy endpoint using a reduced model after dropping disease severity and baseline PD seems appropriate. The reviewer's analysis using a reduced model after dropping disease severity and baseline PD generated a p-value of 0.0486 when Minocycline PTS was compared with S/RP and a p-value of 0.0004 when Minocycline PTS was compared with vehicle, that is, the results remained almost unchanged.***

3. *In both sponsor and reviewer's analyses the center effect was found to be statistically significant, however, no significant treatment by center interaction was found. This indicated that there were significant differences among centers in the reduction of PD, however, the responses were parallel among treatment groups. Graphical representation by the reviewer showed that the effects were parallel in every center (except for center 107, where the mean reduction in PD in Minocycline PTS and S/RP crossed between visit 5 and 6). Center 104 had the highest reduction in mean PD (-1.78 mm, -1.43 mm, and –1.76 mm for Minocycline PTS, Vehicle, and S/RP, respectively) and center 107 had the lowest reduction in mean PD (-0.20 mm, -0.19 mm, and –0.29 mm for Minocycline PTS, Vehicle, and S/RP, respectively). The analysis results also showed the age effect as statistically significant.*

4. *Sponsor did not submit results of test for normality and homogeneity of variances of residuals (two essential assumptions for the validity of ANCOVA). The reviewer's analysis showed p=0.0841 for Shapiro-Wilks test of normality, which indicates that the assumption of normality is not violated.*

5. *For checking robustness of the efficacy results the reviewer carried out an analysis similar to that of the sponsor based on the ranks of change from baseline in PD. The results of the analysis were as follows:*

   a. *ANCOVA p-value to compare Minocycline with S/RP = 0.0628*
   b. *ANCOVA p-value to compare Minocycline with Vehicle = 0.0006*

6. *Following the medical officer's (Dr. John Kelsey) request, a further analysis of the data was performed by the reviewer using the percent change from baseline in PD and similar model of ANCOVA as used for original values of change from baseline PD. The results of this analysis were as follows:*

   a. *ANCOVA p-value to compare Minocycline with S/RP = 0.0651*
   b. *ANCOVA p-value to compare Minocycline with Vehicle = 0.0010*

6.2.2 Analysis of PD change from baseline in evaluable patients

Table 3 shows the sponsor's results of analysis of PD change from baseline in evaluable patients. Data were analyzed using the similar model as the sponsor used for analysis in ITT population.

Table 3: Comparisons of mean change from baseline in PD at 9 months in evaluable patients using ANCOVA (Study 103A)

PATIENT'S AVERAGE POCKET DEPTH	DESCRIPTIVE STATISTIC	TREATMENT DROUPS MINOCYCLINE PTS 110	VEHICLE 111	S/RP 112	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
BASELINE	n	110	111	112	0.962	0.777
	MEAN (STD DEV)	5.90 (0.54)	5.92 (0.55)	5.89 (0.50)		
	MEDIAN	5.80	5.73	5.73		
	RANGE					
CHANGE FROM BASELINE MONTH 9	N	110	111	112	0.014*	<.001**
	MEAN (STD DEV)	-1.24 (0.79)	-0.92 (0.71)	-1.04 (0.78)		
	MEDIAN	-1.25	-0.77	-1.02		
	RANGE					

Source: Table 3.2.2, p. 101, vol. 101 of the sponsor's submission

The results show statistically significant reduction in PD in the Minocycline PTS group compared to both vehicle and S/RP.

6.3 Secondary efficacy

6.3.1 Clinical response

Tables 4 summarizes the sponsor's results of clinical response.

Table 4: Comparisons of mean clinical response at 9 months using ANCOVA (Study 103A)

PATIENT'S PERCENT OF BASELINE TREATMENT SITES WITH	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 121	VEHICLE 123	S/RP 124	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
PD REDUCTION >= 1 mm AT MONTH 9	n	121	123	124	0.111	0.003**
	MEAN (STD DEV)	62.63 (26.92)	53.51 (25.49)	58.47 (27.62)		
	MEDIAN	66.67	52.38	62.50		
	RANGE					
PD REDUCTION >= 2 mm AT MONTH 9	n	121	123	124	0.091	<.001**
	MEAN (STD DEV)	35.69 (25.81)	25.26 (22.92)	31.32 (26.55)		
	MEDIAN	30.00	20.00	24.46		
	RANGE					
PD REDUCTION >= 3 mm AT MONTH 9	n	121	123	124	0.223	0.006**
	MEAN (STD DEV)	13.32 (17.41)	8.61 (11.74)	11.36 (16.91)		
	MEDIAN	6.67	4.55	5.26		
	RANGE					

Source: Table 3.10.1, p. 113, vol. 101 of the sponsor's submission

Difference in mean clinical response in Minocycline PTS group is significant compared to vehicle but is not significant when compared to S/RP.

Reviewer's comments: Following the medical officer's (Dr. John Kelsey) request the reviewer compared the percentage of treated sites with reduction in PD more than a specified threshold. Table 4A in the appendix shows the results. Pairwise comparisons

showed statistically significant differences between Minocycline, and S/RP or Vehicle treatment group for each threshold value.

6.3.2 PD extent score

Table 5 summarizes the sponsor's results of PD extent score.

Table 5: Comparisons of mean PD extent score at 9 months using ANCOVA (Study 103A)

PATIENT'S PERCENT OF BASELINE TREATMENT SITES WITH	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 121	VEHICLE 123	S/RP 124	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
PD >= 5 mm AT BASELINE	N	121	123	124	N/A	N/A
	MEAN (STD DEV)	100 (0.0)	100 (0.0)	100 (0.0)		
PD >= 6 mm AT BASELINE	N	121	123	124	0.580	0.408
	MEAN (STD DEV)	48.99 (16.91)	50.79 (19.77)	49.95 (16.51)		
PD >= 7 mm AT BASELINE	N	121	123	124	0.715	0.395
	MEAN (STD DEV)	16.33 (14.52)	18.03 (17.56)	15.34 (15.12)		
CHANGE FROM BASELINE						
PD >= 5 mm n AT MONTH 9	MEAN (STD DEV)	121 -53.30 (26.26)	123 -43.36 (27.16)	124 -49.08 (28.06	0.111	0.001**
PD >= 6 mm n AT MONTH 9	MEAN (STD DEV)	121 -27.20 (19.91)	123 -22.31 (20.49)	124 -25.00 (21.65)	0.129	0.008**
PD >= 7 mm n AT MONTH 9	MEAN (STD DEV)	121 -7.66 (12.11)	123 -5.34 (11.17)	124 -4.17 (11.55)	0.006**	0.010**

Source: Table 3.7.1 – 3.7.3, p. 109 –111, vol. 101 of the sponsor's submission

Differences in mean percent change from baseline in PD extent score in Minocycline PTS group are significant compared to vehicle at every level and compared to S/RP at level ≥7 mm only.

6.3.3 Bleeding on probing

Table 6 summarizes the sponsor's results of bleeding on probing.

Table 6: Comparisons of mean percentage of patients with bleeding on probing at 9 months using ANCOVA (Study 103A)

PATIENT'S PERCENT BLEEDING ON PROBING	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 121	VEHICLE 123	S/RP 124	P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
BASELINE	N	121	123	124	0.593	0.650
	MEAN (STD DEV)	87.90 (15.17)	87.65 (12.98)	87.25 (14.84)		
CHANGE FROM BASELINE						
MONTH 9	N	121	123	124	0.970	0.012*
	MEAN (STD DEV)	-26.42 (25.29)	-19.14 (22.33)	-26.72 (27.47)		

Source: Table 3.5, p. 107, vol. 101 of the sponsor's submission

Difference in mean change from baseline in percentage of patients with bleeding on probing in Minocycline PTS group is significant compared to vehicle but not compared to S/RP.

6.3.4 Clinical Attachment Level (CAL)

Tables 8 summarizes the results of sponsor's analyses of CAL.

Table 8: Comparisons of mean change from baseline in CAL at 9 months using ANCOVA (Study 103A)

PATIENT'S AVERAGE CLINICAL ATTACHMENT LEVEL	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 121	VEHICLE 123	S/RP 124	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
BASELINE	n	121	123	124	0.6624	0.7988
	MEAN (STD DEV)	5.57 (1.07)	5.52 (1.06)	5.64 (1.08)		
	MEDIAN	5.56	5.55	5.63		
	RANGE					
MONTH 9	n	121	123	124	0.577	0.062
	MEAN (STD DEV)	0.93 (0.81)	0.76 (0.83)	0.91 (0.99)		
	MEDIAN	0.92	0.74	0.83		
	RANGE					

Source: Table 7.1, p. 176, vol. 101 of the sponsor's submission

Reviewer's comments:

1) The reviewer noticed some errors in the change from baseline values of CAL in the submitted data. For example, for patient number 1080901 the sponsor reported the CAL at baseline equal to 4.8636 and CAL at 9 months equal to 4.0000. The corresponding change from baseline was reported as –0.4444. Assuming that the CAL readings at 9 months are correct, the actual change from baseline is –0.8636. There were 217 such cases in different visits, effecting 118 patients. The reviewer recalculated the change from baseline in CAL and performed similar analyses as were performed on change from baseline in PD.

2) In sponsor's data set, patient number 1040362 in S/PR treatment group, had baseline CAL equal to 7.60 mm and visit 6 CAL equal to 0.35 mm, showing a reduction of 7.25 mm. The medical officer (Dr. Kelsey) and the reviewer concluded that this must be an error in the data. Therefore, the reviewer analyzed the data after dropping this data point. The summary of reviewer's analysis is given in Table 9.

Table 9: Comparisons of change from baseline in CAL at 9 months using ANOVA (Study 103A)

PATIENT'S AVERAGE CLINICAL ATTACHMENT LEVEL	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 121	VEHICLE 123	S/RP 124	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
BASELINE	n	121	123	124	0.662	0.798
	MEAN (STD DEV)	5.56 (1.07)	5.51 (1.06)	5.63 (1.06)		
	MEDIAN	5.56	5.55	5.63		
	RANGE					
MONTH 9	n	121	123	123	0.508	0.135
	MEAN (STD DEV)	-1.01(0.82)	-0.87(0.87)	-0.98(0.88)		
	Median	-0.97	-0.75	-0.94		
	RANGE					

Results did not show statistically significant differences in mean change from baseline in CAL when Minocycline PTS was compared with S/PR or vehicle. Table 5A in the appendix shows reviewer's results by subgroup. In making inferences from this table one needs to keep in mind that 1) The study was not powered for the comparison of mean changes in CAL, 2) An adjustment for multiple testing would be required. In general the differences in reduction in CAL between Minocycline PTS and S/RP or vehicle are not statistically significant in any sub-group.

6.4 Sub-group analysis

The sponsor performed analyses of the primary efficacy endpoint using some subgroup patients based on the number of treated sites at baseline. The sub groups were 1) patients with < 20 sites, 2) patients with <40 sites, 3) patients with ≥ 40 sites, 5) patients with <50 sites, and 5) patients ≥ 50 sites. Results show that Minocycline PTS was most efficacious in <40 sites and <50 sites sub-groups (Tables 3.11.7 – 3.11.11, p. 121-125, vol. 101 of the sponsor's submission).

Reviewer's comments: Reviewer performed additional sub-group analyses of change from baseline in PD based on gender, smoking habit, baseline PD, age and baseline severity. The analyses were performed using the method of ANCOVA with treatment, smoking status, baseline disease condition and pooled center as factors, and baseline PD and age as the covariates. Table 6A in the appendix shows the results of these analyses. In making inferences from this table one needs to keep in mind that 1) The study was not powered for the comparison of mean changes in CAL, 2) An adjustment for multiple testing would be required. In general the results showed that the differences in reduction of PD between Minocycline PTS and vehicle in sub-groups with age>50 years, baseline PD≥5 mm, and PD≥6 mm were statistically significant.

7. Results of data analysis (Study 103B)

7.1 Demographic parameters

Table 9A in the appendix shows the sponsor's summary of demographic parameters. The sponsor did not perform statistical analysis to compare the demographic parameters.

Reviewer's comment: Table 9A shows that the Minocycline PTS group had a relatively higher percentage of patients with more than 50 years of age compared to vehicle or S/RP (44.5% 30.2.0%, and 33.3% in Minocycline PTS, vehicle, and S/RP, respectively). The Fisher Exact test performed by the reviewer showed statistically significant difference in these percentages between Minocycline PTS and vehicle.

7.2 Primary efficacy analysis

7.2.1 Analysis of PD change from baseline in the ITT patients

Table 10 shows the sponsor's results of the analyses of the primary efficacy end point, change from baseline in PD, in ITT population.

Table 10: Comparisons of mean change from baseline in PD at 9 months in ITT population using ANCOVA (Study 103B)

PATIENT'S AVERAGE POCKET DEPTH	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 128	VEHICLE 126	S/RP 126	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
BASELINE	n	128	126	126	0.946	0.353
	MEAN (STD DEV)	5.81 (0.42)	5.82 (0.48)	5.79 (0.37)		
	MEDIAN	5.70	5.70	5.70		
	RANGE					
MONTH 9	n	128	126	126	<.001**	<.001**
	MEAN (STD DEV)	-1.63 (0.80)	-1.30 (0.81)	-1.32 (0.80)		
	MEDIAN	-1.71	-1.32	-1.33		
	RANGE					

Source: Table 3.2.1, p. 95, vol. 107 of the sponsor's submission

The result shows highly statistically significant reduction in PD in the Minocycline PTS group compared to both vehicle and S/RP. The magnitude of mean reduction in PD in Minocycline PTS group is 0.31 mm over S/RP and 0.33 mm over vehicle.

Additional non-parametric analysis of the primary efficacy endpoint using the CMH test also showed highly statistically significant ($p<0.001$) reduction in PD in the Minocycline PTS group compared to both S/RP and vehicle.

Reviewer's comment:

1. *The reviewer's analysis on primary efficacy end point confirmed the sponsor's results.*
2. *As was mentioned in Section 4, for the analysis of primary efficacy the sponsor used the method of ANCOVA with treatment group, pooled center, disease severity, and smoking status as factors and baseline PD and age as covariates. However, similar to study 103A, sponsor's results showed that the effects of disease severity and baseline PD were not statistically significant. Therefore, a reanalysis of the primary efficacy endpoint using a reduced model after dropping disease severity and baseline PD seems appropriate. The reviewer's analysis using a reduced model after dropping disease severity and baseline PD generated a p-value < 0.001 when Minocycline PTS was compared with S/RP or with vehicle. The results remained unchanged.*

3. *In both sponsor and reviewer's analyses the center effect was found to be statistically significant, however, no significant treatment by center interaction was found. This indicates that there were significant differences among centers in the reduction of PD, however, the responses were parallel among treatment groups. Graphical representation by the reviewer showed that the effects were parallel in every center. Center 206 had the highest reduction in mean PD (-2.49 mm, -2.07 mm, and –1.97 mm for Minocyline PTS, Vehicle, and S/RP, respectively), and centers 202 had the lowest reduction in mean PD (-0.54 mm, -0.46 mm, and –0.21 mm for Minocycline PTS, vehicle, and S/RP, respectively). The analysis results also showed the age effect as statistically significant.*

4. *Sponsor did not submit results of test for normality and homogeneity of variances of residuals (two essential assumptions for the validity of ANCOVA). The reviewer's analysis showed p=0.8635 for Shapiro-Wilks test of normality, which indicates that the assumption of normality is not violated.*

5. *For checking robustness of the efficacy results the reviewer carried out an analysis similar to that of the sponsor based on the ranks of change from baseline in PD. The results of the analysis were as follows:*

   a. *ANCOVA p-value to compare Minocycline with S/RP <0.001*
   b. *ANCOVA p-value to compare Minocycline with Vehicle <0.001*

6. *Following the medical officer's (Dr.John Kelsey) request, a further analysis of the data was performed by the reviewer using the percent change from baseline in PD and following similar model of ANCOVA as used for original values of change from baseline PD. The results of this analysis were as follows:*

   a. *ANCOVA p-value to compare Minocycline with S/RP <0.001*
   b. *ANCOVA p-value to compare Minocycline with Vehicle < 0.001*

7.2.2 Analysis of PD change from baseline in evaluable patients.

Table 11 shows the sponsor's results of analysis of PD change from baseline in evaluable patients. Data were analyzed using the similar model as the sponsor used for analysis in ITT population.

Table 11: Comparisons of mean change from baseline in PD at 9 months in evaluable patients using ANCOVA (Study 103B)

PATIENT'S AVERAGE POCKET DEPTH	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 118	VEHICLE 111	S/RP 106	P-VALUES MINOCYCLINE PTS vs. S/RP	P-VALUES MINOCYCLINE PTS vs. VEHICLE
BASELINE	N	118	111	106	0.889	0.391
	MEAN (STD DEV)	5.80 (0.42)	5.79 (0.47)	5.80 (0.38)		
	MEDIAN	5.69	5.67	5.70		
	RANGE					
MONTH 9	N	118	111	106	<.001**	<.001**
	MEAN (STD DEV)	-1.64 (0.83)	-1.30 (0.76)	-1.39 (0.78)		
	MEDIAN	-1.72	-1.30	-1.41		
	RANGE					

Source: Table 3.2.2, p. 96, vol. 107 of the sponsor's submission

The results show highly statistically significant reduction in PD in the Minocycline PTS group compared to both vehicle and S/RP.

7.3 Secondary efficacy

7.3.1 Clinical response

Table 12 summarizes the sponsor's results of clinical response.

Table 12: comparisons of mean clinical response at 9 months using ANCOVA (Study 103B)

PATIENT'S PERCENT OF BASELINE TREATMENT SITES WITH	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 128	VEHICLE 126	S/RP 126	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. VEHICLE
PD REDUCTION >= 1 mm AT MONTH 9	n	128	126	126	<.001**	<.001**
	MEAN (STD DEV)	80.66 (21.59)	68.95 (27.15)	69.81 (27.93)		
	MEDIAN	88.15	74.34	77.03		
	RANGE					
PD REDUCTION >= 2 mm AT MONTH 9	n	128	126	126	<.001**	<.001**
	MEAN (STD DEV)	53.08 (28.89)	40.06 (29.36)	41.85 (28.69)		
	MEDIAN	53.55	34.78	38.80		
	RANGE					
PD REDUCTION >= 3 mm AT MONTH 9	n	128	126	126	0.010**	0.004**
	MEAN (STD DEV)	19.12 (19.67)	13.37 (16.31)	13.96 (15.84)		
	MEDIAN	11.88	7.62	8.27		
	RANGE					

Source: Table 3.10.1, p. 107, vol. 107 of the sponsor's submission

Differences in clinical response in Minocycline PTS group are statistically significant compared to both vehicle and S/RP.

Reviewer's comments: Following the medical officer's (Dr. John Kelsey) request the reviewer compared the percentage of sites with reduction in PD more than a specified threshold. Table 10A in the appendix shows the results. Pairwise comparisons showed statistically significant differences between Minocycline, and S/RP or Vehicle for each threshold value, except between Minocycline and vehicle in patients with at least 4.5 mm improvement.

7.3.2 PD extent score

Table 13 summarizes the sponsor's results of PD extent score.

Table 13: Comparisons of mean PD extent score at 9 months using ANCOVA (Study 103B)

PATIENT'S PERCENT OF BASELINE TREATMENT SITES WITH	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 128	VEHICLE 126	S/RP 126	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
PD >= 5 mm AT BASELINE	n	128	126	126	N/A	N/A
	MEAN	100.00	100.00	100.00		
PD >= 6 mm AT BASELINE	N	128	126	126	0.864	0.998
	MEAN (STD DEV)	49.39 (16.90)	48.57 (18.87)	49.20 (15.56)		
PD >= 7 mm AT BASELINE	N	128	126	126	0.866	0.484
	MEAN (STD DEV)	14.69 (13.96)	14.70 (14.42)	14.28 (12.81)		
CHANGE FROM BASELINE						
PD >= 5 mm n AT MONTH 9 MEAN (STD DEV)		128	126	126	<.001**	<.001**
		-70.22 (24.53)	-59.78 (28.83)	-58.95 (28.52)		
PD >= 6 mm n AT MONTH 9 MEAN (STD DEV)		128	126	126	0.006**	<.001**
		-36.23 (19.33)	-28.65 (20.55)	-31.71 (19.83)		
PD >= 7 mm n AT MONTH 9 MEAN (STD DEV)		128	126	126	0.216	0.010**
		-8.56 (11.99)	-6.09 (12.29)	-7.20 (11.22)		

Source: Table 3.7.1 – 3.7.3, p. 104-106, vol. 107 of the sponsor's submission

Differences in mean percent change from baseline in PD extent score in Minocycline PTS group are statistically significant compared to vehicle at every level and compared to S/RP at level ≥5 mm and ≥7.

7.3.3 Bleeding on probing

Table 14 summarizes the sponsor's results of bleeding on probing.

Table 14: Comparison of patient's percent bleeding on probing change from baseline at 9 months using the ANCOVA (Study 103B)

PATIENT'S PERCENT BLEEDING ON PROBING	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 128	VEHICLE 126	S/RP 126	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
BASELINE	n	128	126	126	0.556	0.473
	MEAN (STD DEV)	85.08 (20.08)	86.41 (19.96)	86.41 (19.02)		
	MEDIAN	94.74	95.97	95.33		
	RANGE					
CHANGE FROM BASELINE MONTH 9	n	128	126	126	0.123	<.001**
	MEAN (STD DEV)	-31.63 (27.21)	-22.83 (27.50)	-27.63 (27.58)		

Source: Table 3.5, p. 102, vol. 107 of the sponsor's submission

Difference in mean percent change from baseline in bleeding on probing in Minocycline PTS group is statistically significant compared to vehicle but not compared to S/RP.

7.3.4 Clinical Attachment Level (CAL)

Tables 15 summarize the results of sponsor's analyses of CAL.

Table 15: Comparisons of mean change from baseline in CAL at 9 months using ANCOVA (Study 103B)

PATIENT'S AVERAGE CLINICAL ATTACHMENT LEVEL	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 128	VEHICLE 126	S/RP 126	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	VEHICLE
BASELINE	n	128	126	126	0.283	0.130
	MEAN (STD DEV)	5.21 (1.61)	5.24 (1.71)	5.23 (1.71)		
	MEDIAN	5.43	5.39	5.37		
	RANGE					
MONTH 9	n	128	126	126	0.056	0.008**
	MEAN (STD DEV)	1.04 (1.00)	0.85 (0.94)	0.90 (0.94)		
	MEDIAN	0.93	0.66	0.82		
	RANGE					

Source: Table 7.1, p. 167, vol. 107 of the sponsor's submission

Reviewer's comments:

Similar to study 103A, the reviewer noticed some errors in the change from baseline values of CAL in the submitted data. For example, for patient number 2010017 the sponsor reported the CAL at baseline equal to 3.3013 and CAL at 9 months equal to 3.6333. The corresponding change from baseline was reported as 0.2945. Assuming that the CAL readings at 9 months are correct, the actual change from baseline is –

0.3320. There are 250 such cases in different visits effecting 134 patients. The reviewer recalculated the change from baseline in CAL and performed similar analyses as were performed on change from baseline in PD. The summary of reviewer's analysis is given in Table 16.

Table 16: Comparison of change from baseline in CAL at 9 months using ANOVA (Study 103B)

PATIENT'S AVERAGE CLINICAL ATTACHMENT LEVEL	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 128	VEHICLE 126	S/RP 126	TREATMENT COMPARISON P-VALUES MINOCYCLINE PTS vs. S/RP	MINOCYCLINE PTS vs. VEHICLE
BASELINE	n	128	126	126	0.2826	0.1299
	MEAN (STD DEV)	5.21 (1.60)	5.24 (1.71)	5.23 (1.71)		
	MEDIAN	5.43	5.39	5.37		
	RANGE					
MONTH 9	n	128	126	126	0.1582	0.0124
	MEAN (STD DEV)	-1.09(1.03)	-0.92(0.94)	-0.99(1.01)		
	Median	-0.92	-0.72	-0.88		
	RANGE					

The results of table 16 show statistically significant difference in mean change from baseline in CAL when Minocycline PTS is compared with vehicle. Table 12A in the appendix shows the reviewer's results by subgroup. In making inferences from this table one needs to keep in mind that 1) The study was not powered for the comparison of mean changes in CAL, 2) An adjustment for multiple testing would be required. In general the differences in reduction in CAL between Minocycline PTS and S/RP or vehicle are not statistically significant in any sub-group.

7.4 Sub-group analysis

Sponsor performed analyses of the primary efficacy using some subgroup patients, based on the number of treated sites at baseline. The sub groups were 1) patients with < 20 sites, 2) patients with <40 sites, 3) patients ≥ 40 sites, 5) patients with <50 sites, and 5) patients ≥ 50 sites. Results show that Minocycline PTS was most efficacious in <40 sites and <50 sites sub-groups (Study 103B. Table 3.11.7 – 3.11.11, p. 115-119, vol. 107 of the sponsor's submission).

Reviewer's comments: Reviewer performed additional sub-group analyses of change from baseline in PD based on gender, smoking habit, baseline PD, age and baseline severity. The analyses were performed using the method of ANCOVA with treatment, smoking status, baseline disease condition and pooled center as factors, and baseline PD and age as the covariates. Tables 11A in the appendix show the results of these analyses. In making inferences from this table one needs to keep in mind that In making inferences from this table one needs to keep in mind that 1) The study was not powered for the comparison of mean changes in CAL, 2) An adjustment for multiple testing would be required. In general the results showed that the differences in reduction of PD between Minocycline PTS and S/RP or vehicle in females, non-smokers, sub-group with baseline PD between 5 mm to 6mm were statistically

significant. The results also showed significant difference in reduction of PD between Minocycline PTS and vehicle in sub-group with moderate disease condition

8. Safety

Table 17 summarizes the sponsor's results of number of patients and AEs in different types in the combined data of 103A and 103B.

Table 17: Number of patients and AEs in different categories (Integrated studies 103A and 103B)

AE Type		Minocycline PTS	S/RP + Vehicle	S/RP
		249	249	250
Treatment Emergent	Number of Patients	170 (68.3%)	179 (71.9%)	156 (62.4%)
	Number of AEs	549	589	544
Treatment Emergent Treatment Related	Number of Patients	30 (12.1%)	42 (16.9%)	6 (2.4%)
	Number of AEs	62	75	10
Serious AEs	Number of Patients	6 (2.4%)	6 (2.4%)	5 (2.0%)
	Number of AEs	7	6	5
AEs Leading to Discontinuation of Study	Number of Patients	4 (1.6%)	4 (1.6%)	5 (2.0%)
	Number of AEs	4	5	8

Source: Table 6.2.1.1, p.15, Table 6.12.1, p. 96, Table 6.13.1, p. 100, Table 6.14.1, p. 102, vol. 117 of the sponsor's submission

Serious AEs included body pain, tachycardia, myocardial infraction, colitis, pancreatitis, asthma, urinary incontinence, uterine disorder, accidental injury, carcinoma, hernia, viral infection, embolus, elective surgery, and prostatic carcinoma. None of these were considered drug related. The most common treatment emergent AE was periodontities, occurring in 54 (21.7%), 70 (28.1%), and 64 (25.6%) patients. The sponsor did not perform any analysis of this data.

Reviewer's comment: Reviewer compared the percentage of patients experienced AEs in Minocycline PTS group with S/RP and vehicle group in different AE types, using the Fisher Exact test. The tests showed statistically significant difference in the incidence of treatment emergent treatment related AEs between Minocycline PTS and S/RP groups (P<0.001).

9. Summary and conclusion

The sponsor presented the results of two phase 3 studies (103A and 103B) to claim safety and efficacy of treatment of adult periodontitis in the reduction of pocked depth (PD) by S/RP + Minocycline. The primary efficacy endpoint was the change from baseline in PD at 9 months. The sponsor used the analysis of covariance (ANCOVA) method as the primary analysis and the Cochran- Mantel-Haenszel (CMH) test as supportive analysis to analyze the primary efficacy endpoint.

The sponsor's results from the ANCOVA analysis showed statistically significant differences in the reduction of PD between Minocycline PTS and S/RP in both studies ($p=0.045$ and $p<0.001$ in studies 103A and 103B, respectively). The CMH test showed

statistically significant differences in the reduction of PD between Minocycline PTS and S/RP in study 103B ($p<0.001$), but not in study 103A ($p=0.057$). The magnitudes of mean reductions in Minocycline PTS group over S/RP are 0.16 mm and 0.31 mm in study 103A and study 103B, respectively. In addition, the results of the analysis showed that reduction in PD of Minocycline PTS is significantly greater than that of S/RP + vehicle in both studies ($p<0.001$ for both studies).

Reviewer performed alternative ANCOVA for both 103A and 103B studies, using the ranks of the PD change from baseline. The results from the rank ANCOVA are comparable to sponsor's supportive analysis using the CMH test.

In the combined data of 103A and 103B, there were 6 patients in each of the Minocycline PTS and vehicle group, and 5 patient in S/RP group who had at least one serious AEs . The most common treatment emergent AE was periodontities, occurring in 54 (21.7%), 70 (28.1%), and 64 (25.6%) patients in Minocycline PTS, vehicle, and S/RP treatment groups, respectively.

11/13/2000

M. Atiar Rahman, Ph.D.
Mathematical Statistician, Biometrics III

11.13.2000

Concur: For Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:

Archival NDA 50-781
HFD-540/Division File
HFD-540/Dr. Wilkin
HFD-540/Dr. Kelsey
HFD-540/Dr. Gilkes
HFD-540/Ms. Bhatt

HFD-725/ Chron
HFD-725/ Dr. Huque
HFD-725/ Dr. Alosh
HFD-725/ Dr. Rahman

This review contains 31 pages.

Appendix

Table 1A: Summary of patient recruitment by center
(Study 103A)

		MINOCYCLINE PTS 121			VEHICLE 123			S/RP 124			
CENTER	INVESTIGATOR	SMOKERS	NON-SMOKERS	TOTAL	SMOKERS	NON-SMOKERS	TOTAL	SMOKERS	NON-SMOKERS	TOTAL	OVERALL TOTAL
101	ORINGER	10	8	18	11	8	19	11	9	20	57
102	CATON	9	10	19	9	11	20	8	9	17	56
103	COCHRAN	8	11	19	7	11	18	8	11	19	56
104	FIORELLINI	6	12	18	5	13	18	5	13	18	54
105	PERSSON	6	10	16	6	10	16	6	12	18	50
106	ARMITAGE	1	2	3	2	2	4	1	2	3	10
107	GIANNOBILE	2	3	5	2	4	6	1	4	5	16
108	JOHNSON	4	5	9	3	5	8	4	5	9	26
109	MAGNUSSON	5	9	14	5	9	14	6	9	15	43

Source: Table 2.4, p. 98, vol. 101 of the sponsor's submission

Table 2A: Summary of withdrawal from Study 103A

NUMBER (%) OF PATIENTS	MINOCYCLINE PTS 121		VEHICLE 123		S/RP 124	
TOTAL NUMBER OF DISCONTINUATIONS	6	(5.0%)	11	(8.9%)	10	(8.1%)
DISCONTINUATIONS AMONG SMOKERS	4	(7.8%)	3	(6.0%)	6	(12.0%)
DISCONTINUATIONS AMONG NONSMOKERS	2	(2.9%)	8	(11.0%)	4	(5.4%)
REASON						
ADVERSE EVENT	0	(0.0%)	1	(0.8%)	0	(0.0%)
PROTOCOL VIOLATION	0	(0.0%)	2	(1.6%)	0	(0.0%)
WITHDRAWAL OF CONSENT	1	(0.8%)	1	(0.8%)	3	(2.4%)
FEMALE BECAME PREGNANT	0	(0.0%)	0	(0.0%)	0	(0.0%)
LOST TO FOLLOW-UP	3	(2.5%)	6	(4.9%)	6	(4.8%)
PATIENT RESCUE	0	(0.0%)	0	(0.0%)	0	(0.0%)
OTHER	2	(1.7%)	1	(0.8%)	1	(0.8%)

Source: Table 8, p. 178, vol. 101 of the sponsor's submission

Table 3A: Summary of demographic parameters
(Study 103A)

CHARACTERISTIC	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 121		VEHICLE 123		S/RP 124	
GENDER							
MALE	n (%)	69	(57.0%)	67	(54.5%)	67	(54.0%)
FEMALE	n (%)	52	(43.0%)	56	(45.5%)	57	(46.0%)
AGE (YRS)	n	121		123		124	
<= 50	n (%)	71	(58.7%)	80	(65.0%)	83	(66.9%)
> 50	n (%)	50	(41.3%)	43	(35.0%)	41	(33.1%)
	MEAN	48.6		47.7		48.0	
	STD DEV	10.1		9.7		10.0	
	MEDIAN	47.0		47.0		47.0	
	RANGE	(29, 76)		(29, 77)		(31, 76)	
RACE							
CAUCASIAN	n (%)	99	(81.8%)	92	(74.8%)	95	(76.6%)
BLACK	n (%)	10	(8.3%)	18	(14.6%)	12	(9.7%)
ASIAN	n (%)	4	(3.3%)	3	(2.4%)	3	(2.4%)
HISPANIC	n (%)	7	(5.8%)	10	(8.1%)	10	(8.1%)
OTHER	n (%)	1	(0.8%)	0	(0.0%)	4	(3.2%)
DISEASE SEVERITY							
MODERATE	n (%)	69	(57.0%)	69	(56.1%)	75	(60.5%)
ADVANCED	n (%)	52	(43.0%)	54	(43.9%)	49	(39.5%)
SMOKING STATUS							
YES	n (%)	51	(42.1%)	50	(40.7%)	50	(40.3%)
NO	n (%)	70	(57.9%)	73	(59.3%)	74	(59.7%)

Source: Table 2.2, p. 94, vol. 101 of the sponsor's submission

Table 4A: Comparisons of percentage of treated dental sites with PD change from baseline by at least as indicated by the cut off point (Study 103A)

Cut off point	Treatment	Number of sites with more Reduction in PD than the cut off point	Number of treated sites at baseline	Percentage	Treatment comparison P-value Mino. vs. S/RP	Mino. vs. Vehicle
-1	MINOCYCLINE	2258	3633	62.15	<0.001	<0.001
	VEHICLE	1880	3614	52.02		
	S/RP	1875	3368	55.67		
-1.5	MINOCYCLINE	1588	3633	43.71	<0.001	<0.001
	VEHICLE	1172	3614	32.43		
	S/RP	1265	3368	37.56		
-2	MINOCYCLINE	1326	3633	36.50	<0.001	<0.001
	VEHICLE	927	3614	25.65		
	S/RP	1046	3368	31.06		
-2.5	MINOCYCLINE	720	3633	19.82	<0.001	<0.001
	VEHICLE	465	3614	12.87		
	S/RP	532	3368	15.80		
-3	MINOCYCLINE	548	3633	15.08	<0.001	<0.001
	VEHICLE	315	3614	8.72		
	S/RP	417	3368	12.38		
-3.5	MINOCYCLINE	266	3633	7.32	<0.001	<0.001
	VEHICLE	142	3614	3.93		
	S/RP	164	3368	4.87		
-4	MINOCYCLINE	178	3633	4.90	<0.001	<0.001
	VEHICLE	96	3614	2.66		
	S/RP	112	3368	3.33		
-4.5	MINOCYCLINE	96	3633	2.64	<0.001	<0.001
	VEHICLE	36	3614	1.00		
	S/RP	46	3368	1.37		

Reviewer's table

Numbers of patients are 121, 123, and 124 in Minocycline PTS, Vehicle and S/RP groups, respectively.

Table 5A: Comparisons of mean CAL change from baseline by subgroup at 9 months using ANCOVA (Study 103A)

POPULATION	STATISTICS	MINOCYCLINE	VEHICLE	S/RP	P-Value Mino vs. S/RP	P-Value Mino vs. Veh.
All	N	121	123	123	0.5081	0.1346
	MEAN	-1.01	-0.87	-0.98		
Male	N	69	67	67	0.9892	0.5155
	MEAN	-0.97	-0.88	-1.00		
Female	N	52	56	57	0.2583	0.1047
	MEAN	-1.07	-0.86	-0.95		
NON SMOKER	N	70	73	74	0.8794	0.2198
	MEAN	-1.12	-0.94	-1.15		
SMOKER	N	51	50	50	0.1882	0.3257
	MEAN	-0.87	-0.77	-0.72		
AGE<=50	N	71	80	83	0.4564	0.4607
	MEAN	-1.05	-0.89	-0.95		
AGE>50	N	50	43	41	0.8479	0.1329
	MEAN	-0.97	-0.83	-1.03		
PD_B0*>=5	N	121	123	123	0.5081	0.1346
	MEAN	-1.01	-0.87	-0.98		
PD_B0>=6	N	45	46	34	0.1228	0.0197
	MEAN	-1.29	-0.88	-0.91		
PD_B0>=7	N	3	5	4	0.6552	0.7159
	MEAN	-0.98	-0.85	-1.22		
5<=PD_B0<=6	N	78	78	93	0.8163	0.7325
	MEAN	-0.88	-0.88	-0.98		
6<=PD_B0<=7	N	42	41	30	0.2035	0.0352
	MEAN	-1.31	-0.88	-0.87		
Moderate disease cond.	N	69	69	75	0.4240	0.3796
	MEAN	-1.10	-0.83	-1.23		
Severe disease cond.	N	52	54	49	0.0595	0.2099
	MEAN	-0.89	-0.92	-0.58		

Reviewer's table

* PD_B0 = Baseline pocket depth

Table 6A: Comparisons of mean PD change from baseline by subgroup at 9 months using ANCOVA (Study 103A)

POPULATION	STATISTICS	MINOCYCLINE	VEHICLE	S/RP	P-Value Mino vs. S/RP	P-Value Mino vs. Veh.
All	N	121	123	124	0.0448	0.0004
	MEAN	-1.20	-0.90	-1.04		
Male	N	69	67	67	0.0765	0.0313
	MEAN	-1.17	-0.91	-0.99		
Female	N	52	56	57	0.3265	0.0059
	MEAN	-1.25	-0.89	-1.11		
NON SMOKER	N	70	73	74	0.5303	0.0013
	MEAN	-1.30	-0.93	-1.24		
SMOKER	N	51	50	50	0.0075	0.0785
	MEAN	-1.07	-0.85	-0.76		
AGE<=50	N	71	80	83	0.2518	0.1277
	MEAN	-1.19	-0.99	-1.06		
AGE>50	N	50	43	41	0.0616	0.0001
	MEAN	-1.22	-0.74	-1.00		
PD_B0*>=5	N	121	123	124	0.0448	0.0004
	MEAN	-1.20	-0.90	-1.04		
PD_B0>=6	N	45	46	34	0.0383	0.0001
	MEAN	-1.40	-0.77	-0.91		
PD_B0>=7	N	3	5	4	0.8544	0.7923
	MEAN	-1.91	-0.46	-1.10		
5<=PD_B0<=6	N	78	78	93	0.1724	0.0947
	MEAN	-1.11	-0.99	-1.08		
6<=PD_B0<=7	N	42	41	30	0.0638	0.0008
	MEAN	-1.36	-0.80	-0.88		
Moderate disease cond.	N	69	69	75	0.9583	0.0702
	MEAN	-1.21	-0.90	-1.20		
Severe disease cond.	N	52	54	49	0.0061	0.0056
	MEAN	-1.19	-0.90	-0.8		

Reviewer's table

* PD_B0 = Baseline pocket depth

Table 7A: Summary of patient recruitment by center (Study 103B)

		MINOCYCLINE PTS 128			VEHICLE 126			S/RP 126			
CENTER	INVESTIGATOR	SMOKERS	NON-SMOKERS	TOTAL	SMOKERS	NON-SMOKERS	TOTAL	SMOKERS	NON-SMOKERS	TOTAL	TOTAL
201	DRISKO	9	12	21	9	12	21	10	11	21	63
202	GENCO	5	12	17	6	12	18	4	13	17	52
203	KILLOY	5	7	12	6	6	12	6	7	13	37
204	LAMSTER	7	13	20	4	12	16	6	11	17	53
205	PAQUETTE	3	12	15	5	11	16	4	11	15	46
206	VAN DYKE	4	16	20	3	15	18	4	14	18	56
207	[redacted]MS	2	3	5	2	4	6	2	4	6	17
208	[redacted]RANSKY	0	2	2	1	2	3	0	2	2	7
209	WOLFF	4	12	16	4	12	16	5	12	17	49

Source: Table 2.4, p. 93, vol. 107 of the sponsor's submission

Table 8A: Summary of withdrawal from Study 103B

NUMBER (%) OF PATIENTS	MINOCYCLINE PTS 128		VEHICLE 126		S/RP 126	
TOTAL NUMBER OF DISCONTINUATIONS	6	(4.7%)	8	(6.3%)	11	(8.7%)
DISCONTINUATIONS AMONG SMOKERS	1	(2.6%)	3	(7.5%)	7	(17.1%)
DISCONTINUATIONS AMONG NONSMOKERS	5	(5.6%)	5	(5.8%)	4	(4.7%)
REASON						
ADVERSE EVENT	1	(0.8%)	0	(0.0%)	0	(0.0%)
PROTOCOL VIOLATION	1	(0.8%)	0	(0.0%)	0	(0.0%)
WITHDRAWAL OF CONSENT	1	(0.8%)	4	(3.2%)	2	(1.6%)
FEMALE BECAME PREGNANT	0	(0.0%)	0	(0.0%)	0	(0.0%)
LOST TO FOLLOW-UP	3	(2.3%)	4	(3.2%)	7	(5.6%)
PATIENT RESCUE	0	(0.0%)	0	(0.0%)	1	(0.8%)
OTHER	0	(0.0%)	0	(0.0%)	1	(0.8%)

Source: Table 8, p. 169, vol. 107 of the sponsor's submission

Table 9A: Summary of demographic parameters (Study 103B)

CHARACTERISTIC	DESCRIPTIVE STATISTIC	MINOCYCLINE PTS 128		VEHICLE 126		S/RP 126	
GENDER							
MALE	n (%)	65	(50.8%)	77	(61.1%)	65	(51.6%)
FEMALE	n (%)	63	(49.2%)	49	(38.9%)	61	(48.4%)
AGE (YRS)	n	128		126		126	
<= 50	n (%)	71	(55.5%)	88	(69.8%)	84	(66.7%)
> 50	n (%)	57	(44.5%)	38	(30.2%)	42	(33.3%)
	MEAN	49.6		46.7		47.4	
	STD DEV	10.2		10.3		9.5	
	MEDIAN	48.5		45.0		47.0	
	RANGE	(29, 75)		(29, 79)		(29, 72)	
RACE							
CAUCASIAN	n (%)	96	(75.0%)	89	(70.6%)	96	(76.2%)
BLACK	n (%)	20	(15.6%)	21	(16.7%)	17	(13.5%)
ASIAN	n (%)	5	(3.9%)	6	(4.8%)	8	(6.3%)
HISPANIC	n (%)	5	(3.9%)	7	(5.6%)	4	(3.2%)
OTHER	n (%)	2	(1.6%)	3	(2.4%)	1	(0.8%)
DISEASE SEVERITY							
MODERATE	n (%)	77	(60.2%)	87	(69.0%)	81	(64.3%)
ADVANCED	n (%)	51	(39.8%)	39	(31.0%)	45	(35.7%)
SMOKING STATUS							
YES	n (%)	39	(30.5%)	40	(31.7%)	41	(32.5%)
NO	n (%)	89	(69.5%)	86	(68.3%)	85	(67.5%)

Source: Table 2.2, p. 89, vol. 107 of the sponsor's submission

Table 10A: Comparisons of percentage of treated dental sites with PD change from baseline by at least as indicated by the cut off point (Study 103B)

Cut off point	Treatment	Number of sites with more reduction in PD than the cut off point	Number of treated sites at baseline	Percentage	Treatment comparison P-value Mino. vs. S/RP	Treatment comparison P-value Mino. vs. Vehicle
-1	MINOCYCLINE	3259	4083	79.82	<0.001	<0.001
	VEHICLE	2960	4274	69.26		
	S/RP	2837	3997	70.98		
-1.5	MINOCYCLINE	2407	4083	58.95	<0.001	<0.001
	VEHICLE	2070	4274	48.43		
	S/RP	1982	3997	49.59		
-2	MINOCYCLINE	2082	4083	50.99	<0.001	<0.001
	VEHICLE	1710	4274	40.01		
	S/RP	1692	3997	42.33		
-2.5	MINOCYCLINE	952	4083	23.32	<0.001	<0.001
	VEHICLE	719	4274	16.82		
	S/RP	752	3997	18.81		
-3	MINOCYCLINE	704	4083	17.24	<0.001	<0.001
	VEHICLE	524	4274	12.26		
	S/RP	553	3997	13.84		
-3.5	MINOCYCLINE	260	4083	6.37	0.003	<0.001
	VEHICLE	187	4274	4.38		
	S/RP	193	3997	4.83		
-4	MINOCYCLINE	170	4083	4.16	0.015	<0.001
	VEHICLE	120	4274	2.81		
	S/RP	125	3997	3.13		
-4.5	MINOCYCLINE	63	4083	1.54	0.021	0.462
	VEHICLE	57	4274	1.33		
	S/RP	38	3997	0.95		

Reviewer's table

Numbers of patients is 128, 126, and 126 in Minocycline PTS, Vehicle and S/RP groups, respectively.

Table 11A: Comparisons of mean change from baseline in CAL by subgroup at 9 months using ANCOVA (Study 103B)

POPULATION	STATISTICS	MINOCYCLINE	VEHICLE	S/RP	P-Value Mino vs. S/RP	P-Value Mino vs. Veh.
All	N	128	126	126	0.1596	0.0171
	MEAN	-1.09	-0.92	-0.99		
Male	N	65	77	65	0.8779	0.5948
	MEAN	-0.92	-0.96	-0.89		
Female	N	63	49	61	0.0351	0.0036
	MEAN	-1.26	-0.85	-1.10		
NON SMOKER	N	89	86	85	0.3469	0.0117
	MEAN	-1.20	-0.98	-1.15		
SMOKER	N	39	40	41	0.5116	0.8793
	MEAN	-0.84	-0.79	-0.65		
AGE<=50	N	71	88	84	0.3836	0.1529
	MEAN	-1.10	-0.99	-1.02		
AGE>50	N	57	38	42	0.4313	0.0907
	MEAN	-1.08	-0.75	-0.93		
PD_B0*>=5	N	128	126	126	0.1596	0.0171
	MEAN	-1.09	-0.92	-0.99		
PD_B0>=6	N	37	40	25	0.0844	0.1468
	MEAN	-1.23	-1.18	-1.22		
PD_B0>=7	N	2	3	2	0.6890**	0.4042**
	MEAN	-1.87	-1.24	-2.80		
5<=PD_B0<=6	N	93	87	101	0.3482	0.1037
	MEAN	-1.04	-0.82	-0.93		
6<=PD_B0<=7	N	36	37	23	0.1252	0.4697
	MEAN	-1.14	-1.18	-1.08		
Moderate disease cond.	N	77	87	81	0.4921	0.0766
	MEAN	-1.14	-1.06	-1.16		
Severe disease cond.	N	51	39	45	0.5323	0.2730
	MEAN	-1.02	-0.60	-0.69		

Reviewer's table

* PD_B0 = Baseline pocket depth
** Collapsing all centers

Table 12A: Comparisons of mean PD change from baseline by subgroup at 9 months using ANCOVA (Study 103B)

POPULATION	STATISTICS	MINOCYCLINE	VEHICLE	S/RP	P-Value Mino vs. S/RP	P-Value Mino vs. Veh.
ALL	N	128	126	126	0.0001	0.0001
	MEAN	-1.63	-1.30	-1.32		
MALE	N	65	77	65	0.0145	0.0133
	MEAN	-1.55	-1.32	-1.26		
FEMALE	N	63	49	61	0.0009	0.0011
	MEAN	-1.72	-1.27	-1.39		
NON SMOKER	N	89	86	85	0.0006	0.0002
	MEAN	-1.71	-1.38	-1.38		
SMOKER	N	39	40	41	0.0713	0.0982
	MEAN	-1.46	-1.13	-1.20		
AGE<=50	N	71	88	84	0.0122	0.0046
	MEAN	-1.66	-1.37	-1.41		
AGE>50	N	57	38	42	0.0041	0.0093
	MEAN	-1.59	-1.13	-1.14		
PD_B0*>=5	N	128	126	126	0.0001	0.0001
	MEAN	-1.63	-1.30	-1.32		
PD_B0>=6	N	37	40	25	0.0256	0.1211
	MEAN	-1.69	-1.46	-1.33		
PD_B0>=7	N	2	3	2	*	*
	MEAN	-2.84	-1.11	-1.72		
5<=PD_B0<=6	N	93	87	101	0.0010	0.0005
	MEAN	-1.60	-1.24	-1.32		
6<=PD_B0<=7	N	36	37	23	0.0390	0.2528
	MEAN	-1.66	-1.49	-1.30		
MODERATE DISEASE COND.	N	77	87	81	0.0101	0.0005
	MEAN	-1.62	-1.33	-1.43		
SEVERE DISEASE COND.	N	51	39	45	0.0153	0.0531
	MEAN	-1.65	-1.24	-1.13		

Reviewer's table

*Sample size too small to calculate p-values

* PD_B0 = Baseline pocket depth

Bhatt, Kalyani

From: Ghosh, Tapash
Sent: Friday, February 16, 2001 12:35 PM
To: Bhatt, Kalyani
Cc: Bashaw, Edward D
Subject: Minocycline (NDA 50-781)

Hi Kalyani:

Biopharm does not have any Phase 4 commitment attached to the review. Thanks,

Tapash